REMARKS/ARGUMENTS

Applicants thank the Examiner for the interview conducted on July 16, 2004 in which the claims were discussed in relation to the Papac and Hutchens et al. references. As a result of that interview, Applicants have amended claims 31-38, 40-42, and 44-47, and added new claim 48. After entry of the foregoing amendments, claims 31-48 (2 independent claims; 18 total claims) remain pending in the application. Reconsideration is respectfully requested.

The Examiner first rejected claim 41 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Examiner stated that claim 41 is vague and indefinite because it is unclear what relationship exists between the different antibodies and the analyte. More specifically, the Examiner asked whether the different antibodies bind to different epitopes of the analyte or whether one antibody is bound to the other antibody which in turn binds to the analyte. In response to the Examiner's rejection, Applicants have amended claim 41 to specifically recite that the invention includes the step of immobilizing a plurality of different antibodies that are each specific to a different analyte species.

Claims 31, 32, 36, 37, 45 and 46 stand rejected under 35 U.S.C. §102(a) as being anticipated by Papac et al. (Protein Science). In particular, the Examiner states that Papac discloses antibodies immobilized to agarose beads (i.e. a solid substrate) and incubating these beads with antigens for a time period to allow the immobilized antibody to bind to the antigen to form a complex (i.e. post-combination affinity reagent). The Examiner further states that Papac discloses centrifuging the complex and removing supernatant and adding matrix to the antibody/antigen complex. Finally, the Examiner states that Papac discloses determining the identity of the analyte using mass spectrometry and a mass to charge ratio. Applicants respectfully traverse this rejection.

Papac (Protein Science) discloses the epitope mapping of a known and purified protein and it is known that a specific pure analyte is in the sample to start with. In contrast, Applicants' method is directed to determining whether or not a physiological specimen (such as blood, urine, saliva, etc.) contains an analyte species. In Papac, the authors are studying the interaction of the antibody and their technique is used solely for anticlonal antibodies. In contrast, the antibody interaction in Applicants' method is constant and the goal is to determine whether an analyte species is present in the sample. Papac does not actually teach a method for determining whether

an analyte species is present. Accordingly, Papac fails to teach each of the elements of Applicants' claimed invention and therefore cannot anticipate Applicants' claimed invention.

Claims 31 and 36 stand rejected under 35 U.S.C. §102(e) as being anticipated by Hutchens et al., U.S. Patent No. 5,894,063. In particular, the Examiner states that Hutchens et al. discloses a method for the detection of analytes where the analyte of interest can be captured by immobilized antibodies. The Examiner further states that Hutchens et al. discloses that the antibodies are immobilized to solid surfaces and that the captured analytes can be washed to remove any contaminants and then transferred to a probe surface. Finally, the Examiner states that Hutchens et al. discloses that the analytes can be detected and determined by mass analysis. Applicants respectfully traverse this rejection.

Hutchens et al. discloses a mass spectrometer probe and a method of using the probe for desorption and ionization of analytes. The probe includes a layer of energy absorbing molecules on its surface that are free of analyte and analyte is then applied to the layer of energy absorbing molecules. The analyte can be desorbed by a high energy source and detected in the mass spectrometer. Clearly, Hutchens et al. teaches putting media and captured analyte onto a probe tip and then conducting mass spectrometry. In contrast, Applicants sample on which mass spectrometry is conducted does not include an affinity reagent. Instead, Applicants' claims are directed to capturing and isolating an analyte species using an affinity reagent where the affinity reagent includes an antibody immobilized to a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and then detecting the presence of the isolated and released analyte species using mass spectrometry. Accordingly, in that Hutchens et al. fails to disclose each and every element of Applicants' claimed invention, Hutchens et al. cannot anticipate Applicants' claimed invention.

Claims 33 and 38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Rampal et al., U.S. Patent No. 5,437,979. In particular, the Examiner states that Papac only differs from the instant invention in failing to teach combining the affinity reagent with a specimen using a micropipette tip in which there is a filter element which retains the affinity reagent. The Examiner further contends that Rampal discloses a micropipette tip in which solid substrates are retained by porous frits and that the solid substrates include immobilized reactants which bind to an analyte of interest. The Examiner also states that Rampal discloses that the use of the micropipette tips in this manner minimizes exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed

environment thereby enhancing reliability, reproducibility and safety. Therefore, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate the beads of Papac into a micropipette such as that taught by Rampal to arrive at Applicants' claimed invention. Applicants respectfully traverse this rejection.

As previously discussed above, Papac (Protein Science) fails to teach a method for determining whether an analyte is present in a physiological sample and instead is directed to a method that studies the interaction of a known purified sample. Accordingly, it would not have been obvious to one of ordinary skill in the art to combine Papac and Rampal to arrive at Applicants' claims 33 and 38.

Claims 34 and 39 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Papac (Analytical Chemistry). In particular, the Examiner states Papac (Protein Science) only differs from the instant invention by failing to disclose adding a disassociation agent to the isolated post-combination affinity reagent prior to the step of adding the laser desorption/ionization agent. The Examiner then states that Papac (Analytical Chemistry) discloses that sample preparation can influence the spectra observed and that for immobilized affinity chromatography, a three times stronger signal is observed when the supernatant is used for analysis compared with mixing the MALDI matrix with the beads on the target and that immobilized affinity chromatography differs from conventional chromatography in that it exploits specific biological interactions such as those of an antibody and antigen which demonstrate high specificity associated affinity binding and that, either half of a biological interaction can be used in the stationary phase as an immobilized ligand. The Examiner then contends that it would have been obvious to one of ordinary skill in the art to incorporate the use of a disassociation reagent as taught by Papac (Analytical Chemistry) into the method of Papac (Protein Science) because Papac (Analytical Chemistry) shows that this disassociation reagent allows for a three times stronger signal. Applicants respectfully traverse this rejection.

As previously discussed above, Papac (Protein Science) fails to disclose a method for determining whether an analyte is present in a physiological sample and instead is directed to a method that studies the interaction of a known purified sample. Accordingly, it would not have been obvious to one of ordinary skill in the art to combine Papac (Protein Science) and Papac (Analytical Chemistry) to arrive at Applicants' claims 34 and 39.

Claims 35 and 40 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Papac (Analytical Chemistry) as applied to claims 31, 32, 34,

36, 37, 39, 45 and 46 above, and further in view of Rampal et al. In particular, the Examiner states that Papac (Protein Science) and Papac (Analytical Chemistry) differ from the instant invention only by failing to teach combining the affinity reagent with a specimen using a micropipette tip in which there is a filter element which retains the affinity reagent. The Examiner then states that Rampal discloses a micropipette tip in which solid substrates are retained by porous frits and that the solid substrates comprise immobilized reactants which bind to an analyte of interest. The Examiner then contends that it would have been obvious to one of ordinary skill in the art to incorporate the beads of Papac (Protein Science) into a micropipette such as taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays to minimize exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment, thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection.

As previously discussed above, Papac (Protein Science) and Papac (Analytical Chemistry) fail to disclose a method for capturing and isolating an analyte species from a physiological specimen using an affinity reagent that includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Rampal also fails to disclose these elements. Accordingly, neither Papac (Protein Science), Papac (Analytical Chemistry), or Rampal, either alone or in combination, disclose each and every element of Applicants' claimed invention. Therefore, Applicants' claims 35 and 40 would not be obvious to one of ordinary skill in the art in light of Papac (Protein Science), Papac (Analytical Chemistry) and Rampal.

Claims 41 and 47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Bangs et al. (IVD Technology Magazine). In particular, the Examiner states that Papac (Protein Science) differs from the instant invention only in failing to teach different antibodies on a solid substrate to produce the affinity reagent. The Examiner further states that Bangs et al. discloses the adsorption of polyclonal antibodies to microspheres which bind to monoclonal antibodies to form an affinity reagent for an analyte of interest. The Examiner therefore contends that it would have been obvious to one of ordinary skill in the art to incorporate different antibodies as taught in Bangs on the beads of Papac because Bangs shows that the use of two different antibodies and the microsphere provides better activity or recognition of antigen because a second antibody is away from the surface of the microsphere.

Applicants respectfully traverse this rejection.

As previously discussed above, Papac (Protein Science) fails to disclose each and every element of Applicants' claimed invention. In particular, Papac fails to disclose capturing and isolating an analyte species from a physiological specimen using an affinity reagent which includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Bangs also fails to disclose these elements. Therefore, neither Papac (Protein Science) or Bangs, either alone or in combination, discloses each and every element of Applicants' claimed invention. Accordingly, Applicants' claims 41 and 47 would not be obvious to one of ordinary skill in the art in light of Papac (Protein Science) and Bangs.

Claim 42 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Bangs as applied to claims 31, 32, 36, 37, 41, 45 and 46 above, and further in view of Rampal. In particular, the Examiner states that it would have been obvious to one of ordinary skill in the art to incorporate the modified beads of Papac (Protein Science) into a micropipette taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays and also to minimize exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment, thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection. As previously pointed out above, neither Papac, Bangs, or Rampal, either alone or in combination, disclose capturing and isolating an analyte species from a physiological specimen using an affinity reagent which includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Accordingly, it would not have been obvious to one of ordinary skill in the art to combine Papac (Protein Science), Bangs, and Rampal to arrive at Applicants claim 42.

Claim 43 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Bangs et al. as applied to claims 31, 32, 36, 37, 41, 45, and 46 above and further in view of Papac (Analytical Chemistry). In particular, the Examiner states that it would have been obvious to one of ordinary skill in the art to incorporate the use of a disassociation reagent as taught by Papac (Analytical Chemistry) into the modified method of Papac (Protein Science) because Papac (Analytical Chemistry) shows that this disassociation

reagent allows for a three times stronger signal. Applicants respectfully traverse this rejection.

As previously explained above, neither Papac (Protein Science), Papac (Analytical Chemistry), or Bangs, either alone or in combination, disclose capturing and isolating an analyte species from a physiological specimen using an affinity reagent which includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Accordingly, Applicants' claim 43 would not have been obvious to one of ordinary skill in the art in light of Papac (Protein Science), Papac (Analytical Chemistry), and Bangs.

Finally, claim 44 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Protein Science) in view of Bangs et al. and Papac (Analytical Chemistry) as applied to claims 31, 32, 36, 37, 41, 43, 45 and 46 above and further in view of Rampal. In particular, the Examiner states that it would have been obvious to one of ordinary skill in the art to incorporate the modified beads of Papac (Protein Science) into a micropipette such as taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays and also to minimize exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment, thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection.

As previously pointed out above, neither Papac (Protein Science), Bangs, or Papac (Analytical Chemistry), either alone or in combination, disclose capturing and isolating an analyte species from a physiological specimen using an affinity reagent which includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Accordingly, Applicants' claim 44 would not have been obvious to one of ordinary skill in the art in light of Papac (Protein Science), Bangs, and Papac (Analytical Chemistry).

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience. The Commissioner is hereby

authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. **19-2814**. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

By: _____
Laura J. Zeman
Reg. No. 36,078

SNELL & WILMER L.L.P.
One Arizona Center
400 East Van Buren
Phoenix, Arizona 85004-2202
Telephone: (602) 382-6377
Facsimile: (602) 382-6070